Differentiation and characterization of metabolically functioning hepatocytes from human embryonic stem cells.

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Public Summary:

Scientific Abstract:
Human embryonic stem cells (hESCs) may provide a cell source for functional hepatocytes for clinical applications and drug development. Initially, the hESC population was enriched to be more than 85% definitive endoderm (DE) as assessed by the expression of CXCR4, SOX17, and FOXA2. We then successfully converted DE into hepatic progenitors with 93% of the cells being positive for alpha-feto protein within 9 days. The percentage of albumin positive cells gradually increased to 90% at days 20-22 after differentiation. Moreover, our hESC-derived hepatocytes (hEH) developed a complete biotransformation system including phase I and II metabolizing enyzmes and phase III transporters. Nuclear receptors, which are critical in regulating the expression of metabolizing enzymes, were also expressed by our hEH. Using ultraperformance liquid chromatography-tandem mass spectrometry technology, we identified seven metabolic pathways of the drug bufuralol including four newly-reported ones in our hEH, which are the same as those in freshly isolated human primary hepatocytes (hPH). In addition, the results of the metabolism of four drugs indicate that our hEH have the capacity to metabolize these drugs at levels that are comparable to hPH. In conclusion, we have generated a relatively homogenous population of hepatocytes from hESCs, which appear to have complete metabolic function that is comparable to primary liver cells. These results represent a significant step towards the efficient differentiation of mature hepatocytes for cell-based therapeutics as well as for pharmacology and toxicology studies.